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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/705,791	11/10/2003	Kenneth Chien	041673-1202	5197

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EXAMINER	
SGAGIAS, MAGDALENE K	
ART UNIT	PAPER NUMBER
1632	

DATE MAILED: 12/01/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/705,791	CHIEN ET AL.	
	Examiner	Art Unit	
	Magdalene K. Sgagias	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *01 September 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *18,19,23 and 24* is/are pending in the application.

4a) Of the above claim(s) *25-31* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *18,19,23 and 24* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *9/1/06*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicant's arguments filed 9/1/06 have been fully considered but they are not persuasive. The amendment has been entered. Claims 18-19 and 23-24 are pending. Claims 25-31 are withdrawn to non-elected invention. Claims 1-17, 20-22 and 32-35 are canceled. Claims 18-19 and 23-24 are under consideration.

Oath/Declaration

Non-initialed and/or non-dated alterations have been made to the oath or declaration. See 37 CFR 1.52(c). The objection to the Oath/Declaration is withdrawn.

Claim Objections

Claim 23 objections to minor informalities are withdrawn.

Claim Rejections - 35 USC § 112

Claims 18-19, 23-24, rejection under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter, which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention is withdrawn.

Claims 18-19, 23-24 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter, which was not

described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Claims are directed to a method for treating heart failure associated with the loss of cardiac muscle contractility by delivering an expression vector encoding a phospholaban molecule having a single point mutation consisting of S16E or a double point mutation consisting of K3ER14E to myocytes, wherein the expressed molecule accelerates SERCA2 mediated calcium ion transport in the treated myocytes to improve cardiac muscle contractility.

The specification discusses that several single point mutations of phospholamban (PLB), such as R14E (Seq. ID. No. 4) or a double point mutation of PLB, K3E/R14E (Seq. ID. No. 6) transgene can be engineered in order to disrupt the inhibitory effects of PLB on SERCA2a. The specification discloses using recombinant adenoviruses, myocytes which overexpresses V49A, one of the single point mutations in PLB, exhibit an increase in contractility, while myocytes which overexpress the wild-type PLB exhibit a decrease in contractility when compared to non-infected myocytes, invitro, as is documented in Figure 5. The specification also discloses that adult rabbit myocytes are infected with the adenoviral transgenes of LacZ, K3E/R14E, or antisense PLB, there is a significant difference in the number of spontaneously contracting cells between the different groups (LacZ < antisense PLB < K3E/R14E) (specification p 21, lines 20-30, Table 2). While the specification provides teachings pertaining to production of a single point mutation PLB protein consisting of V49 single point mutation of PLB protein, or the K3E/R14E double point mutation of PLB, in adult rabbit myocytes, in vitro, the specification fails to provide any relevant teachings or specific guidance or working examples with regard to the production of said molecules in vivo, by way of the claimed methods, that results in treating heart failure associated with loss of cardiac muscle contractility. The guidance provided by the instant specification fails to correlate the production of a therapeutic protein in vitro to the

production of a therapeutic protein in vivo resulting in treatment of heart failure. Thus, as enablement requires the specification to teach how to make and use the claimed invention, the specification fails to enable the claimed method for treating heart failure associated with the loss of cardiac muscle contractility. It would have required undue experimentation to make and use the claimed invention without a reasonable expectation of success.

As a first issue, the claims are directed to a method for treating cardiac heart failure associated with loss of cardiac muscle contractility in a subject by delivering a construct to cardiac myocytes and producing a therapeutic protein in cardiac myocytes to improve cardiac muscle contractility and thus fall into the realm of gene therapy. The specification has disclosed gene transfer by injecting recombinant adenovirus expressing wild-type and mutant human PLB (sense mutation Val49A), into cardiac myocytes, in vivo, into 1 day old neonatal mouse heart and the isolated cardiac myocytes 4 weeks after injection were identified harboring the mutant transgenes (specification p 28, lines 5-15). However, the specification has not provided any specific guidance or working examples that correlate to treatment of heart failure associated with loss of cardiac muscle contractility. Since the instant specification has failed to provide specific guidance or working examples correlating to treatment of heart failure one of skill in the art could not rely on the state of the gene therapy art to treat heart failure associated with loss of cardiac contractility by way of the claimed methods. This is because the art of gene therapy is an unpredictable art with respect myocardial cell targeting, levels of expression of a therapeutic protein necessary to provide therapy, and mode of administration of the therapeutic gene. Cardiomyocytes, being post-mitotic and terminally differentiated cells, present their own unique challenges and several methods for myocardial gene delivery each presents its own limitations and benefits (**Thompson et al,** Annals of Medicine, 36(Suppl 1): 106-115, 2004) (p 109). For example, direct myocardial injection is burdened with the delivered gene expressing only in and

around the small region of myocardium surrounding the needle tack, or pericardial injection is an effective means of transfection in rats and could be proved useful for minimally invasive human delivery if large animal models show similar results (**Thompson et al,** (p 109). With respect to use of viral vectors for cardiac gene transfer **Thompson** reports several limitations such as short duration of expression, small insert capacity, difficulty in production of high tier stock, low ability to infect non-dividing cells and low efficiency of transfection (p 111, and Table 1). Thus, while progress has been made in recent years for gene transfer in vivo, vector targeting to cardiomyocytes in the heart tissue in vivo continues to be unpredictable and inefficient as supported by numerous teachings available in the art. **Barbato et al,** (Critical Reviews in Clinical Laboratory Sciences, 40(5): 499-545, 2003) while reviewing the status of the role of gene therapy in the treatment of cardiovascular diseases notes the challenge of gene therapy is the actual delivery of the genetic material into the targeted tissue in sufficient quantities to result in the synthesis of adequate quantities of gene product to elicit the desired therapeutic action while limiting systemic and/or local toxicity (p 501, under vectors). Vectors differ in transfection efficiency, immunogenicity and ability to transduce dividing or quiescent cells (**Barbato et al,** p 501, 2nd paragraph under vectors). For example, the transient nature of transgene expression with adenoviral vectors may limit the use of these vectors to the treatment of acute vascular injury and have less utility in treating chronic or progressive disorders such as heart failure and atherosclerosis (**Barbato et al,** p 504, 2nd paragraph). **Beck et al,** (Current Gene Therapy,4: 457-467, 2004) reports the technical challenges related to cardiovascular gene transfer are still significant with respect to (i) efficiency of gene delivery, (ii) achievement of high and stable level of transgene expression in a specific cell-type and (iii) design and administration tools and vectors that are safe for clinical application (p 463, bridge 1st to 2nd column). Therefore the prior art challenges the underlying assumption that the single- or double

point mutated PLB transgene will be expressed at sufficient therapeutic levels at the targeted cardiomyocytes, in vivo, wherein transgene expression accelerates SERCA2 mediated calcium ion transport in the treated cardiomyocytes to improve cardiac muscle contractility resulting in the treatment of cardiac failure associated with loss of cardiac muscle contractility.

As a second issue, the claims are directed to treating heart failure by the expression of the PLB mutated transgene into a subject having heart failure associated with the loss of cardiac muscle contractility wherein expression of the PLB mutated transgene accelerates SERC2 mediated calcium ion transport in treated myocytes to improve cardiac muscle contractility. The specification has disclosed gene transfer by injecting recombinant adenovirus expressing wild-type and mutant human PLB (sense mutation Val49A), in vivo, into 1 day old neonatal mouse heart and the isolated myocytes 4 weeks after injection were identified harboring the mutant transgenes (specification p 28, lines 5-15, example 4). The underlying assumption is that the expression of the human mutant PLB transgene in cardiac myocytes, will accelerate SERCA2 mediated calcium ion transport in the treated myocytes resulting in the treatment of heart failure associated with loss of cardiac muscle contractility, in vivo. However, the specification failed to provide guidance and/or specific examples wherein expression of said mutated PLB transgene results in treating heart failure associated with the loss of cardiac muscle contractility in a subject by way of the claimed methods. One of the issues is evaluating the efficacy of gene therapies have been performed in disease-free animal models. For example, despite the growing body of literature supporting the use of gene therapy technology to prevent the intimal hyperplastic response to vascular injury a criticism has been raised is evaluating the efficacy of gene therapy have been performed on in disease-free blood vessels of immunologically naïve animals (**Barbato et al,** p 516-517 under limitations). What remains to be answered is whether animal models of disease accurately predict the response of human

vessel to similar gene therapies (**Barbato et al,** p 517, 1st paragraph). In light of the above the prior art is silent on the treatment of heart failure associated with loss of cardiac muscle contractility by mutated PLB gene therapy taken together with the lack of guidance in the specification and the example 4 which is to a disease-free animal model injected with a mutated PLB do not reasonably predict a favorable outcome and further do not provide any evidence that this approach would treat heart failure associated with loss of cardiac muscle contractility, it would have required undue experimentation to practice the instant invention by way of the claimed method.

Therefore, in view of the quantity of experimentation necessary to determine the parameters listed above for the treatment of a heart failure associated with loss of cardiac muscle contractility, the lack of direction or guidance provided by the specification for treatment of heart failure, the absence of working examples that correlate to the treatment of heart failure, the unpredictable state of the art with respect to gene therapy, and in particular gene transfer *in vivo* to cardiomyocytes, the undeveloped state of the art pertaining to the treatment of heart failure by gene therapy, it would have required undue experimentation for one skilled in the art to make and/or use the claimed invention.

Response to Arguments

Applicants argue that the art has recognized the significance of the inventors' achievement in identifying the S16E mutant PLB molecule that is presently claimed, as demonstrated in the enclosed reference by Crystal, published after filing of the instant application, Crystal noted that "numerous studies have shown that gene therapy can transiently forestall heart failure and now, for first time, Chien (inventor) and his colleagues have demonstrated that experimental heart failure can persistently be prevented with gene therapy"

by referring to the inventors' paper by Hoshijima et al, Nat Med, 2002. Applicants further argue Crystal notes that the inventor and his colleagues were able to persistently express S16E PLB in the heart, they also showed that SE16 PLB gene therapy, despite not addressing the primary cardiac abnormality in the B1014.6 hamsters (as a cure), enhanced a variety of parameters associated with cardiac function. Applicants further argue that Crystal notes the Chien (inventor) study shows that enhancement of SERCA function can be used to treat heart failure caused by other defects. These arguments are not persuasive.

Applicants have not provided guidance to override the issue of unpredictability of treating heart failure by PLB gene therapy as cited by the art at the time of filing of the instant application. The invention must be examined in view of the art as a whole at the time of filing. Further the evidence presented in the Hoshijima et al, Nat Med, 2002 paper, which is published after the filing of the instant application there is no therapeutic effect in cardiomyopathic hamsters after administration of the rAAV/S16E phspholamban but the authors report the transcoronary gene transfer of S16E phospholamban via rAAV vector is a potential therapy for progressive dilated cardiomyopathy and associated heart failure (abstract). As the Applicants argue Crystal also notes the Hoshijima et al, Nat Med, 2002 paper, shows enhancement in a variety of parameters associated with cardiac function. In fact, Crystal also notes the extrapolation of the Chien studies into human studies using this strategy is clearly not yet by a long shot and suggests caution in extrapolating results in specific animal models (p 3, 2nd column).

Applicants argue in accord with the Zhao et al, 2004 review paper of phospholamban in cardiac function the inventor's work has been cited as showed "chronic inhibition of phospolamban (PLN) by delivering a pseudophosphorylated S16E-PLN into the heart to successfully prevented progressive heart failure in inherited cardiomyopathic hamsters and also

rescued the cardiac dysfunction and remodeling induced by myocardial infraction in a model of acquired heart failure". Applicants further argue as predicted in the specification, S16E has activity comparable to that reported for the K3ER1`4E molecule. These arguments are not persuasive.

Applicants have not provided guidance to override the issue of unpredictability of treating heart failure by PLB gene therapy as cited by the art at the time of filing of the instant application. In fact, Zhao while referring to the inventor's work which is published after the filing date of the instant application, goes on to say the inventors' studies validate the premise that inhibition of PLN by gene transfer may represent a new therapeutic modality in heart failure and we should remain cautiously optimistic about the clinical value of gene transfer mediated inhibition of PLN in heart failure, as further basic and clinical research is required (p 214, 1st and 2nd column). Applicant's claims encompass a treatment with a cure effect. There is no enabled use for no effect. In the present situation, lack of guidance provided by the specification amounts to an invitation for the skilled artisan not have been able to predict without undue experimentation whether PLN mutated gene transfer into cardiomyocytes in vivo with the viral vectors of the instant invention would result in the treatment of heart failure associated with loss of cardiac muscle contractility.

Conclusion

No claim is allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after

the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Magdalene K. Sgagias whose telephone number is (571) 272-3305. The examiner can normally be reached on Monday through Friday from 9:00 am to 5:00 pm. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Peter Paras, Jr., can be reached on (571) 272-4517. The fax phone number for the organization where this application or proceeding is assigned is (703) 872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll free).

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